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08/790540

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/790,540	01/30/97	HUSE W	F-IX-2405

18M1/0903

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EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1806	5

DATE MAILED: 09/03/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☒ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.
Of the above, claim(s) 19-25 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-18 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-25 were are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☒ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-421-632/40206

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-18, drawn to vitaxin-specific antibodies and nucleic acids encoding said antibodies, classified in Class 530, subclass 387.1 and Class 536, subclass 23.53.

II. Claims 19-25, drawn to method of treatment with vitaxin-specific antibodies, classified in Class 424, subclass 130.1.

3. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the product as claimed can be used in a materially different process such as immunopurification procedures or detection/diagnostic assays.

4. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II and Groups I and II have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper

5. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

6. During a telephone conversation with David Gay on 7/28/97, a provisional election was made with traverse to prosecute the invention of I, claims 1-18. Affirmation of this election must be made by applicant in responding to this Office action. Claims 19-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

7. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Applicant is reminded to amend the specification to correspond to how the figures will be corrected.

8. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

9. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1- 18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of copending application USSN 08/791,391. Although the conflicting claims are not identical, they are not patentably distinct from each other because each application is drawn to the same or nearly the same vitaxin-specific antibodies and nucleic acid encoding said antibodies and modifications thereof.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-18 are directed to an invention not patentably distinct from claims 1-48 of commonly assigned USSN 08/791,391.

Commonly assigned USSN 08/791,391, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-18 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

Claims 1-48 are indefinite in the recitation of "substantially the same" and "functional fragment thereof" because their characteristics are not known. This language is vague and indefinite since it encompasses many different amino acid and nucleic acid sequences as well as many different forms and modification s and it is not clear from the disclosure which particular "sameness" or "function" are being referred to. There is insufficient information and guidance concerning the metes and bound of said "sameness" and "function" as it relates to the structure and/or function of the vitaxin-specific antibodies and nucleic acids encoding said antibodies. The metes and bounds of said "substantially the same" and "functional fragment thereof" have not been defined in the specification as filed. The term in clam is a relative term which renders the claim indefinite. Further, the terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of recombinant antibodies and nucleic acids encoding said recombinant antibodies broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Both CDRs and framework regions contribute to successful humanization of functional antibodies. An effective number of exposed amino acid residues in framework regions that are consistent with corresponding framework regions of a human antibody do not necessarily correlate with either reduced immunogenicity or functional retention. Often excising out portions of a protein or modifications to a protein would result in deleterious effects to the overall activity and effectiveness of a protein. Applicant has not clearly shown or define the criticality or permissibility of the modifications encompassed by the claims that result in "substantially the same" and "functional fragment thereof" that provide vitaxin-specific antibodies and nucleic acids encoding said antibodies. For example, referring to "substantially the same" is meaningless in the absence of mathematical algorithm employed to calculate such number. Depending on the gap weight, gap length, lengths of two sequences to be compared, etc., a percentage of sequence identity can vary dramatically. Similarly, the absence of reciting a function would encompass undue experimentation in designing "functional fragments", wherein a number of different functions, not all of which are directed to the vitaxin specificity and function intended by the instant invention.

It would require undue experimentation to produce all such possible recombinant antibodies and nucleic acids without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such recombinant antibodies and nucleic acids.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

14. It is apparent that the LM609 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification (claims 1-18). If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that if the claimed and disclosed amino acid sequences or nucleic acid sequences set forth in the instant application encode the entire LM609 antibody, then a deposit for said LM609 antibody (hybridoma) is not required. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin.

15. Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-18 are indefinite in the recitation of "LM609" because its characteristics are not known. The use of "LM609" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "LM609" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines or hybridomas.

As pointed out above in section 14, the disclosure of the sequence for an entire immunoglobulin satisfies the biological deposit of said immunoglobulin and would render the claims definite.

B) Claims 1-18 are indefinite in the recitation of "grafted" because the metes and bounds of said term or the defining structural features are unclear. "Grafted" antibodies is a broad term that encompass any number of recombinant forms of antibodies and applicant has not provided sufficient direction to define said "grafted" forms.

D) The amendments must be supported by the specification so as not to add any new matter.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

17. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

18. An issue of public use or on sale activity has been raised in this application. In order for the examiner to properly consider patentability of the claimed invention under 35 U.S.C. 102(b), additional information regarding this issue is required as follows:

Biotechnology Newswatch (1/16/95 and 2/6/95) disclose the use of LM609 antibody including the humanized version of said antibody. Also it is noted that Cheresh, who developed the LM609 antibody and who conducted the in vivo experiments, is not listed as an inventor.

Applicant is reminded that failure to fully respond to this requirement for information will result in a holding of abandonment.

19. Claims 1 and 15-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brooks et al. (Cell, 1994; 1449). Brooks et al. teach the LM609 antibody of the instant application. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced antibody.

20. Claims 1 and 15-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Choi et al. (J. Vasc. Surg., 1994; 1449). Choi et al. teach the LM609 antibody of the instant application. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced antibody.

21. Claims 1 and 15-18 are rejected under 35 U.S.C. § 102(a)(e) as being anticipated by Kim et al. (U.S. Patent No. 5,578,704). Kim et al. teach the LM609 antibody of the instant application. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced antibody.

22. Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Brooks et al. (Cell, 1994; 1449) or Choi et al. (J. Vasc. Surg., 1994; 1449) or Kim et al. (U.S. Patent No. 5,578,704) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 10-39 or Examples I and II of the instant specification or as cited by references on the 1449. It would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies, given the LM609 antibody and hybridoma and its associated properties known in the prior art. The instant claims are drawn to αvβ3-specific/ vitaxin-specific antibodies and fragments thereof and nucleic acids encoding said antibodies, particularly the LM609 specificity.

Brooks et al. teaches that αvβ3-specific antibodies were important in determining signaling events critical to the survival and differentiation of vascular undergoing angiogenesis in vivo and that integrin αvβ3-specific antagonists such as the LM609 antibody could promote tumor regression (see entire document).

Choi et al. teach the important role of the αvβ3 integrin in smooth muscle cell migration in vitro and neointimal hyperplasia in vivo with αvβ3-specific antagonists, including the LM609 antibody (see entire document).

Kim et al. teaches that αvβ3-specific antibodies were expected to be valuable diagnostic and therapeutic tools in studying the biological role and the structure/functional relationships with its various ligands as well as the LM609 antibody which binds the same epitope as the 23C6 antibody is able to bind the αvβ3 complex and due to ability to inhibit the binding of tumor cells and blood vessel forming endothelial cells to vitronectin, fibrinogen and von Willebrand factor was proposed for use as tumor growth inhibitor (see Background of the Invention). Also, Kim et al. teach the art known generation of recombinant or humanized antibodies and modification thereof for a number of uses (see Detailed Description of the Invention). This reference differs from the instant invention by not teaching the humanization of the LM609 antibody and nucleic acids encoding said antibody per se. However, it was obvious to one of ordinary skill in the art at the time the invention was made to humanize various antibodies, including αvβ3-specific antibodies such as LM609, particularly in view of its specificity and functional properties known at the time the invention was made.

Therefore the primary references clearly teach αvβ3-specific antibodies the instant LM609 specificity and associated properties as valuable diagnostic and therapeutic tools in various biological processes. These references differ from the instant claims by not disclosing the generation of recombinant forms and nucleic acids of the LM609 antibody and hybridoma per se.

Given the availability of the LM609 antibody and hybridoma together with general immunoglobulin gene cloning and expression strategies, it would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609 hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning. The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known LM609 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. The claimed DNA sequences must encode a recombinant antibody comprising heavy and/or light chain variable regions of the LM609 antibody.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.
(703) 305-7939.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 2, 1997